REMARKS

Claims 1-2 and 4-11 are pending. Claim 2 has been canceled. Claims 1, 6, 7 and 8 have been amended without prejudice and without acquiescence. No new matter is entered herein.

The following issues are outstanding in the pending application:

- Claims 1-2, 4-10 and 11 are rejected under 35 U.S.C. § 112, first paragraph; and
- Claims 1-2, 4, and 5 are rejected under 35 U.S.C. § 102(b).

I. Claims 1-2, 4-10 and 11; 35 U.S.C. § 112, first paragraph

Claims 1-2, 4-10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserts that the state of the art before and after the filing of the instant application shows that ADMA could be modulated in other disorders and therefore ADMA levels is not specific to any condition and cannot be relied upon as a marker for the diagnosis of IUGR or pre-eclampsia. Applicants respectfully disagree.

As discussed in the claims above, the invention concerns identifying that a pregnant woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR. Those women or fetuses identified as being "at risk" in accordance with the invention will not necessarily go on to develop pre-eclampsia or IUGR. They will however be monitored closely for any appearance of either disease.

Even if one were to agree that several of the documents cited by the Examiner disclose that ADMA may be elevated by diseases or conditions other than pre-eclampsia or IUGR, as discussed in our last response, pre-eclampsia is a complex, multifactorial disease involving changes in many organ systems. For instance, changes in blood pressure, platelet aggregation, liver function and renal function are typical indices of the disease. The presence of the disorders mentioned by the Examiner in a pregnant woman will almost certainly contribute to the appearance and diagnosis of pre-eclampsia. This is confirmed by Dr Rose in his Declaration.

Given this, an elevated ADMA level can be used to identify pregnant woman as being at risk of developing pre-eclampsia or their fetuses as being at risk of developing IUGR.

In further support of the enablement of the present claims, the Applicants submit a Declaration under 37 C.F.R. §1.132 by Dr. Matthew Rose. Dr. Rose has experience in the prognosis and diagnosis of pre-eclampsia in pregnant women.

Dr. Rose's experience in understanding the pathophysiology of pre-eclampsia stems from studies he carried out for the Degree of Ph.D. at the Institute of Obstetrics & Gynaecology, University of London. His studies were focused on the metabolism of arachidonic acid, a precursor of bioactive molecules such as prostaglandins, in human placenta and fetal membranes with specific reference to pre-eclampsia and premature labor. He has also worked for a start-up company, which was developing a novel diagnostic test for pre-eclampsia based on small molecules which are involved in insulin signaling. In his current post he is involved in a project to develop tests for management of high risk pregnancies. He is therefore familiar with the current literature on pre-eclampsia and also with the opinions of leading researchers in the field. This is confirmed by his curriculum vitae, which is also attached.

The prior art cited *before* the filing of the instant application fails to provide evidence for the lack of predictability. **MPEP 2164.05(a)** states "The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification." Cooke et al. (Circulation. 2004 Apr 20;109(15):1813-8) concludes that ADMA may be an "Über marker" reflecting the summative effect of various risk factors on endothelial health (last sentence of the second paragraph on page 1815). The Cooke reference alone demonstrates that ADMA levels possess the degree of predictability required for using ADMA as a marker.

Fard et al. (Arterioscier Thromb Vasc Biol 2000; 20: 2039-2044) studied fifty patients with type 2 diabetes mellitus at baseline and 5 hours after ingestion of a high-fat meal. The patients included thirty-four men and sixteen women with type 2 diabetes mellitus (aged 42 to 75

years, mean 62±9 years). The subjects were not pregnant woman at a stage of from 4 to 25 weeks gestation, as required by the present claims. Therefore, Fard is not relevant.

Hamasaki et al. (Gen Pharmacol 1997; 28: 653-659) studied the effects of nicotine administration on Japanese White male rabbits. ADMA levels were determined in endothelial cells removed from previously denuded and sham-operated carotid arteries. Hamasaki did not determine ADMA levels in pregnant woman from 4 to 25 weeks of pregnancy. Therefore, the Hamasaki reference is not relevant.

MPEP §2164.01(b) states "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The specification at paragraph **[0024]** of the published disclosure (U.S. Patent Publication No. 2007/0185200) states that the mean plasma ADMA concentration in a normal pregnancy between 4-25 weeks is typically about 0.3 to 0.6μmol/L. As stated in Table 3 and in paragraph **[0089]**, the women who subsequently developed pre-eclampsia had significantly higher levels of ADMA compared to the women who had normal pregnancies (2.7 [2.21-3.21] μmol/L vs. 0.81 [0.49-1.08] μmol/L respectively.) None of the women with normal uterine artery Doppler waveforms (no notches) developed pre-eclampsia and the median plasma ADMA level for women who subsequently developed IUGR and pre-eclampsia was 3.04 and 2.78 μmol/L, respectively. This data demonstrates that a plasma ADMA level measurement of greater than 1.5 μmol/L can be used determine that a woman is at risk of developing IUGR or pre-eclampsia. The specification at paragraph **[0025]** states that an increased plasma level of ADMA greater than about 1.45 μmol/L is associated with increased susceptibility to or risk of developing of pre-eclampsia or increased susceptibility to or risk of developing of IUGR.

Additionally, the Examiner has failed to produce evidence or prior art cited *after* the filing of the instant application by one skilled in the art that states the present invention (measuring asymmetric dimethylarginine (ADMA) in a **pregnant woman** at a stage of pregnancy **from 4 to 25 weeks gestation** to assess the risk of a woman developing pre-eclampsia

or her fetus developing IUGR) is not possible. **MPEP 2164.05(a)** states "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered."

Kielstein et al (Am. J. Kidney Dis. 2005; 46: 186—202) authored a review article which advances the idea that ADMA accumulation may be a cardiovascular risk factor in patients with end-stage renal disease and summarizes the relationship between ADMA and adverse cardiovascular events, including death, in dialysis patients. Kielstein does not state or suggest that it is not possible to determine if a pregnant woman is at risk of developing pre-eclampsia by measuring ADMA in a fluid sample taken at a stage of pregnancy from 4 to 25 weeks gestation. Fang et al (Hypertension 2006; 48: 724-729) studied in an experimental situation the effect of salt loading on normotensive subjects (n=60, aged 20 to 60 years; by a complete history and physical examination). The aims were to determine whether plasma ADMA can be modulated by chronic salt loading in normotensive salt-sensitive persons, to determine ADMA's relationship with NO and to determine if dietary potassium supplementation can reverse any effect. Fang does not state or suggest that it is not possible to determine if a pregnant woman is at risk of developing pre-eclampsia by measuring ADMA in a fluid sample taken at a stage of pregnancy from 4 to 25 weeks gestation. Therefore, the Kielstein and the Fang reference fails to provide evidence that the disclosed invention was not possible at the time of filing.

The Examiner asserts that the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any pregnant woman of any ethnicity suffering form multiple chronic disorders resulting in aberrant expression of ADMA. The Examiner uses Lopez-Jaramillo (J. Hypertens. 2005; 23(6): 1121-9) and Holden et al. to support this assertion. The studies conducted in the Lopez-Jaramillo and/or the Holden reference have no relevance to the patentability of the present invention. Additionally, the Examiner asserts that measuring the level of ADMA in any tissue or fluid does not give the skilled artisan a reasonable expectation of success. ***As described above, a working example is given in the specification describing how to practice the invention in a pregnant woman.*** One of ordinary skill in the art

through routine optimization could easily identify which tissue or fluid would be optimal for monitoring ADMA levels. This type of optimization is as routine as finding the optimal vein for drawing blood.

Finally, the present claims as amended are directed to a method of identifying that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR) by measuring ADMA in a plasma sample and determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.45 μmol/L. The claims are not directed to diagnosing pre-eclampsia or to determining an underlying cause for an increase in ADMA. Therefore, the claims are enabled and the Applicants respectfully request the removal of the rejection of claims 1-2, 4-10 and 11 under 35 U.S.C. § 112, first paragraph.

II. Claims 1-2, 4, and 5; 35 U.S.C. § 102(b)

Claims 1-2, 4, and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Holden et al (Am. J. Obstet. Gynecol. 1998; 178(3):551-6). Applicants respectfully disagree.

As currently submitted, claim 1 reads "A method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring asymmetric dimethylarginine (ADMA) in a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation; and (b) determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.5 μmol/L in the woman."

Holden et al. discloses a study of ADMA levels in women with pre-eclampsia and women without pre-eclampsia. The study does not assess the women's risk of developing pre-eclampsia or their fetuses developing IUGR. Indeed, the women with pre-eclampsia were already diagnosed as having the disease, whereas the control women did not at any stage develop the disease. Additionally, the risk of developing pre-eclampsia was not assessed. Risk is not mentioned at all in the Holden reference. Also, Holden does not disclose or suggest measuring ADMA in a sample taken from a pregnant woman during 4 to 25 weeks gestation to determine if

the woman is at risk of developing preeclampsia. Furthermore, Holden does not teach determining that a woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR when the level of ADMA in the woman is greater than 1.5 μmol/L.

Anticipation of a claim is only established where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987), and Applicants assert that Holden fails to teach all elements of the claims. The present invention claims a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR). The claimed invention requires measuring ADMA in a sample taken from a pregnant woman during 4 to 25 weeks of gestation, and determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.5 μmol/L in the woman. Holden does not disclose determining that a woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.5 μmol/L in the woman. Holden does not teach all elements of claim 1. Therefore, Holden does not anticipate the present claims.

If an independent claim is not anticipated, then any claim depending therefrom is by definition not anticipated. Applicant respectfully submits that claims 2, 4 and 5 depend at least in part from independent claim. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the outstanding rejection of claims 1-2, 4 and 5 under 35 U.S.C. § 102(b) as being anticipated by Holden et al (Am. J. Obstet. Gynecol. 1998; 178(3):551-6). Thus, the claims are erroneously rejected over the Holden reference and the Applicant respectfully requests the rejection be removed.

In view of the above, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response other than the fees for a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114. and a Petition for Extension of Time of

One Month. However, if the fees are deficient, please charge our Deposit Account No. 06-2380, under Order No. HO-P03236US0 from which the undersigned is authorized to draw.

Dated: November 21, 2008

Respectfully submitted,

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